IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, Plaintiffs, v. NATERA, INC., Defendant.	C.A. No. 19-cv-567-CFC-CJB **(CONSOLIDATED)**

FIRST AMENDED COMPLAINT

Plaintiffs CareDx, Inc. ("CareDx") and The Board Of Trustees Of The Leland Stanford Junior University ("Stanford," and collectively with CareDx "Plaintiffs"), for their complaint against Defendant Natera, Inc. ("Natera"), hereby allege as follows:

NATURE OF THE ACTION

1. Years ago, researchers at Stanford University invented a method for determining organ transplant rejection. It allowed doctors to assess rejection through blood tests and without

invasive biopsies. This method is intended to save lives, minimize patient pain and stress, and cut the healthcare costs of treating transplant patients.

2. Stanford University secured the patents to its researchers' invention and licensed the patents exclusively to CareDx. CareDx then brought this invention out of the lab and into the clinical setting, helping leading transplant centers around the country treat patients. CareDx has worked hard on this effort, investing substantially to make this technology widely available.

3. Now, years after Stanford researchers and CareDx put in the research and development work to invent this new method and bring it to the clinical setting, Natera uses CareDx's licensed technology without permission in violation of the patent laws. Natera must be held accountable.

4. Accordingly, this is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, against Defendant Natera.

5. CareDx brings this action to halt Natera's infringement of CareDx's rights under the Patent Laws of the United States 35 U.S.C. § 1, et seq., which arise under U.S. Patent Nos. 9,845,497 ("the '497 patent") (attached as Exhibit 1), 8,703,652 ("the '652 patent") (attached as Exhibit 2), and 10,329,607 ("the '607 patent") (attached as Exhibit 3).

PARTIES

6. CareDx is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 3260 Bayshore Blvd., Brisbane, CA 94005.

7. CareDx was formed in 1998 by pioneers in molecular diagnostics. Since its inception, CareDx has focused its expertise on the discovery, development and commercialization of clinically differentiated, high-value solutions for organ transplant recipients. It was the first company to develop and commercialize non-invasive transplant surveillance testing to monitor transplant recipients' immune status with the aim to improve long-term patient outcomes.

8. Today, CareDx markets and sells AlloSure® ("AlloSure"). AlloSure uses advanced DNA sequencing methods to quantify donor-derived cell-free DNA (dd-cfDNA) in transplant recipients without having to conduct separate genotyping. Measuring dd-cfDNA in a transplant recipient's blood enables early detection of kidney transplant rejection and facilitates personalized immunosuppressive treatment. AlloSure has helped numerous nephrologists manage their patients' post-transplant care, while avoiding the high costs and added risks of renal biopsies.

9. Stanford is a trust possessing corporate power that is organized under the laws of California, with a principal place of business at the Office of the President, Building 10 Main Quad, Stanford, California 94305. Stanford is the patent owner and licensor for the '497, '652, and '607 patents and is joined in the infringement action for these patents because it is a necessary party.

10. On information and belief, Natera is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business at 201 Industrial Road, Suite 410, San Carlos, CA 94070. Natera markets and sells a Kidney Transplant Rejection Test, also described as an "organ transplant rejection assay" and "allograft rejection" test, which it performs at its CLIA-certified laboratory in San Carlos, CA. Exhibit 4.

JURISDICTION AND VENUE

11. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

12. Venue is proper in this Court under 28 U.S.C. §§ 1391 and 1400(b).

13. This Court has jurisdiction over Natera because Natera is a Delaware corporation.

14. This Court also has jurisdiction over Natera because, upon information and belief, Natera, directly or indirectly, uses, offers for sale, and/or sells the Kidney Transplant Rejection Test throughout the United States and in this judicial district.

BACKGROUND

15. Plaintiffs repeat and re-allege the foregoing paragraphs as if set forth specifically herein.

16. On information and belief, in the mid-2018 time frame Natera began preparing to develop and commercialize a Kidney Transplant Rejection Test. According to a Natera press release, "Natera's organ transplant rejection assay is designed to detect active allograft rejection in patients who have undergone renal (kidney) transplantation. The assay works by measuring the fraction of donor-derived cell-free DNA (dd-cfDNA) in the recipient's blood, which can spike relative to background cfDNA when the transplanted organ is injured due to immune rejection. The assay leverages Natera's core single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology, to more accurately measure dd-cfDNA levels without the need for donor genotyping, and it has been clinically validated for test performance independent of donor type, rejection type, and clinical presentation." Exhibit 4.

17. On December 5, 2018, scientists affiliated with Natera listed a clinical trial titled, "Utility of a Novel Dd-cfDNA Test to Detect Injury in Renal Post-Transplant Patients" on the National Institute of Health (NIH) website: clinicaltrials.gov. Exhibit 5. The clinical trial listing states that the intervention/treatment is a diagnostic test called "Natera KidneyScan" and describes the test as "Natera's novel SNP-based mmPCR-NGS test that measures dd-cfDNA" in a transplant recipients' blood to diagnose kidney transplant rejection.

18. On December 23, 2018, scientists affiliated with Natera published an article entitled, "Optimizing Detection of Kidney Transplant Injury by Assessment of Donor-Derived Cell-Free DNA Via Massively Multiplex PCR" (attached hereto as Exhibit 6) in the Journal of Clinical Medicine. On information and belief, this article describes the methodology of Natera's Kidney Transplant Rejection Test. Natera's January 7, 2019 press release confirms that the purpose of the study was to clinically validate the Kidney Transplant Rejection Test methodology: a "donor-derived cell-free DNA (dd-cfDNA) test for active allograft rejection in kidney transplant recipients" which uses "Natera's core single nucleotide polymorphism (SNP)-based massively multiplexed PCR (mmPCR) technology." Exhibit 7.

19. On February 1, 2019, Natera publicly announced a partnership to begin distributing "Natera's kidney transplant rejection test in the United States in collaboration with the company's direct sales team." Exhibit 4. As Natera's CEO explained, the partnership would permit it to "accelerate" Natera's entry into the market. *Id.*

20. Natera infringes, literally or under the doctrine of equivalents, the '497 patent through its activities connected to its performance of the Kidney Transplant Rejection Test and all variants of the Kidney Transplant Rejection Test. For instance, representative Claim 1 of the '497 patent is listed below:

> 1. A method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient, the method comprising:
>
> (a) genotyping a solid organ transplant donor to obtain a single nucleotide polymorphism (SNP) profile of the solid organ transplant donor;
>
> (b) genotyping a solid organ transplant recipient to obtain a SNP profile of the solid organ transplant recipient, wherein the solid organ transplant recipient is selected from the group consisting of: a kidney transplant, a heart transplant, a liver transplant, a pancreas transplant, a lung transplant, a skin transplant, and any combination thereof;
>
> (c) obtaining a biological sample from the solid organ transplant recipient after the solid organ transplant recipient has received the solid organ transplant

from the solid organ transplant donor, wherein the biological sample is selected from the group consisting of blood, serum and plasma, and wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant; and

(d) determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids from the solid organ transplant in at least one assay, wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR), and wherein the at least one assay detects the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample.

21. Performance of Natera's Kidney Transplant Rejection Test and all variants thereof leads to infringement of this claim in the following way. First, a plasma sample containing cell-free DNA (cfDNA) from a kidney transplant recipient (post-transplant) is genotyped to obtain a SNP profile. This involves three steps: (i) cfDNA is extracted from the recipient's plasma sample, (ii) cfDNA is amplified via massively multiplex PCR (mmPCR), and (iii) the amplified SNPs are then subject to next generation sequencing (NGS). Finally, the amount of donor-derived cfDNA (dd-cfDNA) in the post-transplant recipient's plasma is determined by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids. *See* Exhibit 5; Exhibit 6.

22. As an example, attached hereto as Exhibit 8 is a preliminary and exemplary claim chart detailing Natera's infringement of multiple claims of the '497 patent. This chart is not intended to limit Plaintiffs' right to modify this chart or any other claim chart or allege that other activities of Natera infringe the identified claims or any other claims of the '497 patent or any other patents.

23. Natera infringes, literally or under the doctrine of equivalents, the '652 patent through its activities connected to its performance of the Kidney Transplant Rejection Test and all variants thereof. For instance, representative Claim 1 of the '652 patent is listed below:

> 1. A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:
>
> (a) providing a sample comprising cell-free nucleic acids from a subject who has received a transplant from a donor;
>
> (b) obtaining a genotype of donor-specific polymorphisms or a genotype of subject-specific polymorphisms, or obtaining both a genotype of donor-specific polymorphisms and subject-specific polymorphisms, to establish a polymorphism profile for detecting donor cell-free nucleic acids, wherein at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs;
>
> (c) multiplex sequencing of the cell-free nucleic acids in the sample followed by analysis of the sequencing results using the polymorphism profile to detect donor cell-free nucleic acids and subject cell-free nucleic acids; and
>
> (d) diagnosing, predicting, or monitoring a transplant status or outcome of the subject who has received the transplant by determining a quantity of the donor cell-free nucleic acids based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids by the multiplexed sequencing, wherein an increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction or organ failure, and wherein sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV).

24. Performance of Natera's Kidney Transplant Rejection Test and all variants thereof leads to infringement of this claim in the following way. First, a plasma sample containing cell-free DNA (cfDNA) from a kidney transplant recipient (post-transplant) is genotyped to obtain a SNP profile. This involves three steps: (i) cfDNA is extracted from the recipient's plasma sample, (ii) cfDNA is amplified via massively multiplex PCR (mmPCR), and (iii) the amplified SNPs are then subject to next generation sequencing (NGS). Finally, a quantity of donor-derived cfDNA

(dd-cfDNA) in the post-transplant recipient's plasma is determined. Active rejection (AR) can be detected with at least 89% sensitivity. *See* Exhibit 5; Exhibit 6.

25. As an example, attached hereto as Exhibit 9 is a preliminary and exemplary claim chart detailing Natera's infringement of multiple claims of the '652 patent. This chart is not intended to limit CareDx's right to modify this chart or any other claim chart or allege that other activities of Natera infringe the identified claims or any other claims of the '652 patent or any other patents.

26. Natera infringes, literally or under the doctrine of equivalents, the '607 patent through its activities connected to its performance of the Kidney Transplant Rejection Test and all variants thereof. For instance, representative Claim 1 of the '607 patent is listed below:

> 1. A method of quantifying kidney transplant-derived circulating cell-free deoxyribonucleic acids in a human kidney transplant recipient, said method comprising:
>
> (a) providing a plasma sample from said human kidney transplant recipient, wherein said human kidney transplant recipient has received a kidney transplant from a kidney transplant donor, wherein said plasma sample from said human kidney transplant recipient comprises kidney transplant-derived circulating cell-free deoxyribonucleic acid and human kidney transplant recipient-derived circulating cell-free deoxyribonucleic acid;;
>
> (b) extracting circulating cell-free deoxyribonucleic acid from said plasma sample from said human kidney transplant recipient in order to obtain extracted circulating cell-free deoxyribonucleic acid, wherein said extracted circulating cell-free deoxyribonucleic acid comprises said kidney transplant-derived circulating cell-free deoxyribonucleic acid and human kidney transplant recipient-derived circulating cell-free deoxyribonucleic acid;
>
> (c) performing a selective amplification of target deoxyribonucleic acid sequences, wherein said selective amplification of said target deoxyribonucleic acid sequences is of said extracted circulating cell-free deoxyribonucleic acid, wherein said selective amplification of said target deoxyribonucleic acid sequences amplifies a plurality of genomic regions comprising at least 1,000 single nucleotide polymorphisms, wherein said at least 1,000 single nucleotide polymorphisms comprise homozygous single nucleotide polymorphisms, heterozygous single nucleotide polymorphisms, or both homozygous single nucleotide polymorphisms

and heterozygous single nucleotide polymorphisms, and wherein said selective amplification of said target deoxyribonucleic acid sequences is by polymerase chain reaction (PCR; and

(d) performing a high throughput sequencing reaction, wherein said high throughput sequencing reaction comprises performing a sequencing-by-synthesis reaction on said selectively-amplified target deoxyribonucleic acid sequences from said extracted circulating cell-free deoxyribonucleic acid, wherein said sequencing-by-synthesis reaction has a sequencing error rate of less than 1.5%;

(e) providing sequences from said high throughput sequencing reaction, wherein said provided sequences from said high throughput sequencing reaction comprise said at least 1,000 single nucleotide polymorphisms; and

(f) quantifying an amount of said kidney transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient to obtain a quantified amount, wherein said quantifying said amount of said kidney transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient comprises using markers distinguishable between said human kidney transplant recipient and said kidney transplant donor, wherein said markers distinguishable between said human kidney transplant recipient and said kidney transplant donor comprises single nucleotide polymorphisms selected from said at least 1,000 single nucleotide polymorphisms identified in said provided sequences from said high throughput sequencing reaction, and wherein said quantified amount of said kidney transplant-derived circulating cell-free deoxyribonucleic acid in said plasma sample from said human kidney transplant recipient comprises at least 0.03% of the total circulating cell-free deoxyribonucleic acid from said plasma sample from said human kidney transplant recipient.

27. Performance of Natera's Kidney Transplant Rejection Test and all variants thereof leads to infringement of this claim in the following way. First, a plasma sample containing cell-free DNA (cfDNA) from a kidney transplant recipient (post-transplant) has cfDNA extracted from that it includes cfDNA from both the donor and the recipient. Next, target sequences from the extracted cfDNA corresponding to SNPs are selectively amplified using PCR. The amplified SNPs are then subject to next generation sequencing (NGS), and the resulting sequences are used to determine an amount of donor-derived in the post-transplant recipient's plasma. *See* Exhibit 6; Exhibit 7.

28. As an example, attached hereto as Exhibit 10 is a preliminary and exemplary claim chart detailing Natera's infringement of multiple claims of the '607 patent. This chart is not intended to limit Plaintiffs' right to modify this chart or any other claim chart or allege that other activities of Natera infringe the identified claims or any other claims of the '607 patent or any other patents.

COUNT I

(Infringement of U.S. Patent No. 9,845,497)

29. Plaintiffs repeat and re-allege the foregoing paragraphs as if set forth specifically herein.

30. On December 19, 2017, the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 9,845,497 (the "'497 patent"), entitled "Non-Invasive Diagnosis of Graft Rejection in Organ Transplant Patients."

31. Stephen R. Quake, Ph.D., Thomas M. Snyder, Ph.D., and Hannah Valantine, M.D. are the sole and true inventors of the '497 patent. By operation of law and as a result of written assignment agreements, Stanford obtained the entire right, title, and interest to and in the '497 patent.

32. Pursuant to license agreements with Stanford, CareDx obtained an exclusive license to the '497 patent in the field of non-invasive monitoring of organ transplant rejection through cell-free DNA analysis.

33. On information and belief, Natera has infringed and continues to infringe the '497 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the Kidney Transplant Rejection Test. As an example, attached as Exhibit 7 is a preliminary and exemplary claim chart detailing Natera's infringement of the '497 patent. This chart is not intended to limit Plaintiffs' right to modify the chart or allege

that other activities of Natera infringe the identified claims or any other claims of the '497 patent or any other patents.

34. Exhibit 7 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 7 that is mapped to the Kidney Transplant Rejection Test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT II

(Infringement of U.S. Patent No. 8,703,652)

35. Plaintiffs repeat and re-allege the foregoing paragraphs as if set forth specifically herein.

36. On April 22, 2014, the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 8,703,652, entitled "Non-Invasive Diagnosis of Graft Rejection in Organ Transplant Patients."

37. Stephen R. Quake, Ph.D., Thomas M. Snyder, Ph.D., and Hannah Valantine, M.D. are the sole and true inventors of the '652 patent. By operation of law and as a result of written assignment agreements, Stanford obtained the entire right, title, and interest to and in the '652 patent.

38. Pursuant to license agreements with Stanford, CareDx obtained an exclusive license to the '652 patent in the field of non-invasive monitoring of organ transplant rejection through cell-free DNA analysis.

39. On information and belief, Natera has infringed and continues to infringe the '652 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the Kidney Transplant Rejection Test. As an example, attached as Exhibit 8 is a preliminary and exemplary claim chart detailing Natera's infringement

of these claims of the ’652 patent. This chart is not intended to limit Plaintiffs’ right to modify the chart or allege that other activities of Natera infringe the identified claims or any other claims of the ’652 patent or any other patents.

40. Exhibit 8 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 8 that is mapped to Natera’s Kidney Transplant Rejection Test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

COUNT III

(Infringement of U.S. Patent No. 10,329,607)

1. Plaintiffs repeat and re-allege the foregoing paragraphs as if set forth specifically herein.

2. On June 25, 2019, the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 10,329,607 (“the ’607 patent”), entitled “Non-Invasive Diagnosis of Graft Rejection in Organ Transplant Patients.”

3. Stephen R. Quake, Ph.D., Thomas M. Snyder, Ph.D., and Hannah Valantine, M.D. are the sole and true inventors of the ’607 patent. By operation of law and as a result of written assignment agreements, Stanford obtained the entire right, title, and interest to and in the ’607 patent.

4. Pursuant to license agreements with Stanford, CareDx obtained an exclusive license to the ’607 patent in the field of non-invasive monitoring of organ transplant rejection through cell-free DNA analysis.

5. On information and belief, Natera has infringed and continues to infringe the ’607 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the Kidney Transplant Rejection Test. As an example,

attached as Exhibit 10 is a preliminary and exemplary claim chart detailing Natera's infringement of these claims of the '607 patent. This chart is not intended to limit Plaintiffs' right to modify the chart or allege that other activities of Natera infringe the identified claims or any other claims of the '607 patent or any other patents.

6. Exhibit 10 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 10 that is mapped to Natera's Kidney Transplant Rejection Test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

JURY DEMAND

7. CareDx and Stanford demand a jury trial on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, CareDx and Stanford pray that this Court grant the following relief:

A. A judgment that Natera has infringed the '497 patent, '652 patent and/or the '607 patent and that the '497 patent, the '652 patent, and/or the '607 patent are valid.

B. Damages or other monetary relief, including, but not limited to, costs and pre- and post-judgment interest, to Plaintiffs;

C. An order enjoining Natera and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the '497 patent, the '652 patent, and/or the '607 patent;

D. Such further and other relief as this Court deems proper and just, including, but not limited to, a determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Plaintiffs in this action.

Dated: March 12, 2020

Respectfully submitted,

FARNAN LLP

/s/ Michael J. Farnan

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
919 N. Market St., 12th Floor
Wilmington, DE 19801
(302) 777-0300
(302) 777-0301 (Fax)
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Attorneys for Plaintiffs

Of Counsel:

Edward R. Reines
Derek C. Walter
WEIL, GOTSHAL & MANGES LLP
201 Redwood Shores Parkway
Redwood Shores, CA 94065
(650) 802-3000

Stephen Bosco
WEIL, GOTSHAL & MANGES LLP
2001 M St., NW
Suite 600
Washington, DC 20036
(202) 682-7000